UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/600,985	11/13/2000	Edwin L. Madison	TSRI 568.1	5201

7590 09/10/2002

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive
Chicago, IL 60606

EXAMINER
SNEDDEN, SHERIDAN

ART UNIT	PAPER NUMBER
1653	13

DATE MAILED: 09/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/600,985	Applicant(s) MADISON, EDWIN L.	
	Examiner Sheridan K Snedden	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *18-20,22-24,27 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,21,25,26,28 and 30-32* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☒ Claim(s) *1-32* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11/13/2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-17, 21, 25, 26, 28, 30-32 drawn to variant human tissue-type plasminogen activator protein compositions and method of making are, for example, classified in class 530, subclass 350 and class 514, subclass 2.

Group II, claim(s) 18-20, 22-24, 29, drawn to polynucleotides encoding variant human tissue-type plasminogen activator protein, expression vectors and host cells is, for example, classified in class 435, subclass 69.1.

Group III, claim(s) 27, drawn to an antibodies contained in a kit is, for example, classified in class 530, subclass 387.1.

Upon thorough consideration of the claims, the examiner has determined that a lack of unity of invention exists, as defined in Rule 13.

Annex B, Part 1(e), indicates the permissible combinations of different categories of claims. Part 1(e(i)) states that inclusion of an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product, and an independent claim for a use of the said product is permissible. As such, Group I combines a variant human tissue-type plasminogen activator protein compositions and method of making. The remaining claims additional products and lack unity of invention as indicated below.

The inventions listed as Groups I, II and III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or

corresponding special technical features for the following reasons: each recites different products differing in structure, biological function and mode of operation. Because each Group is directed toward different compositions, each has a special technical feature not required by the other. As each Group requires a special technical feature not shared with the other, they lack unity of invention.

2. During a telephone conversation with Michael McCarthy on August 28, 2002 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-17, 21, 25, 26, 28, 30-32. Affirmation of this election must be made by applicant in replying to this Office action. Claims 18-20, 22-24, 27, 29 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Drawings

3. Drawings submitted with the application, sheets 1-4, have been approved by the Draftsman.

Claim Objections

4. Claim 1 is objected to for failing to comply with the sequence rule requirements of 37 CFR 1.821 through 1.825. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). The amino acids in a protein or peptide sequence shall be listed using the three-letter abbreviation with the first letter as an upper case character as set forth in 37 CFR 1.822(d). Full

compliance with the sequence rules is required in response to this Office action. A complete response to this Office action must include both compliance with the sequence rules and a response to the issues set forth in this Office Action. Failure to fully comply with both of these requirements in the time period set forth in this Office action will be held to be non-responsive.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17,21,25,26,28 and 30-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it is unclear as to the meaning of R275 as there is no reference sequence recited in the claim. Additionally, it is unclear as to which aspartate 477 and lysine 429 the claim refers.

Claim 28 is indefinite as to the composition of the kit.

Claim 30 and 31 are indefinite for being dependent on a non-elected claim.

Claims 2-17,21,25,26,28 and 30-32 are indefinite for being dependent on indefinite claim 1.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 5-8, 10-11, 13, 15-16 and 30-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Strandberg *et al.* (J Biol Chem. 1995 Oct 6;270(40):23444-9). Strandberg *et al.* teach a variant human tissue-type plasminogen activator (tPA) wherein Arg-275 and at least one other basic amino acid residue in the serine protease region (defined as amino acids 264 to 527 on page 2 of the specification) is substituted with a non-basic amino acid, which results in the disruption of the salt bridge formed with Asp-477 (regarding claim 1). Specifically, Strandberg *et al.* teach the variant where Arg-275 and Asp-477 is substituted with glutamate and glutamate or glutamine, respectively (regarding claim 2; Strandberg *et al.* use the chymotrypsin numbering system where positions 15 and 195 correspond to 275 and 477, respectively. See footnotes on page 15 of provisional application 60/030,655). The Arg-275-Glu, Asp-477-Glu variant displayed a zymogenicity factor of 10 (Table II on page 23446; regarding claim 2). The Arg-275-Glu, Asp-477-Gln variant displayed a fibrin stimulation factor of 1,050,000 (page 23446, column 2, paragraph 1; regarding claims 5-8) and a fibrin selectivity factor of 190 (page 23446, column 2, paragraph 3; regarding claims 15 and 16). The Arg-275-Glu, Asp-477-Glu variant was less reactive toward PAI-1 by a factor of 13 (page 23447; regarding claims 10-11 and 13). Strandberg *et al.* teach a method of making a variant single chain human tPA comprising a step of culturing a cell and purification of the protein (page 23445; regarding claims 30-31). Thus, the reference anticipates the claims 1, 2, 5-8, 10-11, 13, 15-16 and 30-31 of the current invention.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-17,21,25,26,28 and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strandberg et al. (J Biol Chem. 1995 Oct 6;270(40):23444-9) in further view of Tate *et al.* (Biochemistry. 1987 Jan 27;26(2):338-43), Petersen *et al.* (Biochemistry. 1990 Apr 10;29(14):3451-7), Lamba *et al.* (J Mol Biol. 1996 Apr 26;258(1):117-35), Bennett *et al.* (US Patent No: 5,246,850), Anderson *et al.* (US Patent No: 5,520,913) and Hassouna *et al.* (US Patent No: 5,525,477).

Strandberg *et al.* teach a variant human tissue-type plasminogen activator (tPA) wherein Arg-275 and at least one other basic amino acid residue in the serine protease region (defined as amino acids 264 to 527 on page 2 of the specification) is substituted with a non-basic amino acid, which results in the disruption of the salt bridge formed with Asp-477 (regarding claim 1). Specifically, Strandberg *et al.* teach the variant where Arg-275 and Asp-477 is substituted with glutamate and glutamate or glutamine, respectively (regarding claim 2; Strandberg *et al.* use the chymotrypsin numbering system where positions 15 and 195 correspond to 275 and 477, respectively. See footnotes on page 15 of provisional application 60/030,655). The Arg-275-Glu, Asp-477-Glu variant displayed a zymogenicity factor of 10 (Table II on page 23446; regarding claim 2). The Arg-275-Glu, Asp-477-Gln variant displayed a fibrin stimulation factor

of 1,050,000 (page 23446, column 2, paragraph 1; regarding claims 5-8) and a fibrin selectivity factor of 190 (page 23446, column 2, paragraph 3; regarding claims 15 and 16). The Arg-275-Glu, Asp-477-Glu variant was less reactive toward PAI-1 by a factor of 13 (page 23447; regarding claim 11 and 13). Strandberg *et al.* teach a method of making a variant single chain human tPA comprising a step of culturing a cell and purification of the protein (page 23445; regarding claims 30-31).

Strandberg *et al.* do not teach a variant with a zymogenicity factor of 75 or 100 (regarding claims 3-4), nor a variant that is inhibited by PAI-1 by at least a factor of 200 less compared to wild-type (regarding claims 12, 14 and 17). Stranberg *et al.* do not teach the specific variant of Arg-275-Glu, His-417-Asp, Arg-275-Glu, His-417-Glu or Arg-275-Glu, Lys-429-Tyr (regarding claims 21 and 32). Strandberg *et al.* does not teach a variant for use as a treatment of a thrombotic condition or the dosage required (regarding claims 25 and 26). Strandberg *et al.* does not teach the use of the variant in a diagnostic kit (regarding claim 28).

Tate *et al.* teach a variant human tissue-type plasminogen activator (tPA) wherein Arg-275 is substituted with a non-basic amino acid, glycine (see Abstract). Tate *et al.* teach that the above substitution prevents plasmin mediated cleavage of tPA into the active two chain form, and thus, the one-chain form of tPA persist. Tate *et al.* teach that fibrin bound significantly more of the mutated one-chain form compared to the others forms of the enzyme that were tested. Tate *et al.* teach that with the addition of cofactors, the mutated one-chain form has equivalent activity when compared to the activated two-chain form, resulting is a zymogenicity factor of 20 to 50 (page 341, line 2). The above mutant tPA also binds to fibrin with increase specificity compared to the wild-type tPA tested (page 341, second full paragraph). Tate *et al.* teach a

method of making a variant single chain human tPA comprising a step of culturing a cell and purification of the protein (page 339; regarding claims 30-31).

Petersen *et al.* teach a variant human tissue-type plasminogen activator (tPA) wherein Arg-275 is substituted with a non-basic amino acid glycine, and a variant human tissue-type plasminogen activator wherein Lys-416 and His-417 are substituted with the non-basic amino acids serine and threonine, respectively. Peterson *et al.* teach that the salt bridge formation between Asp-477 and basic residues Lys-277, Lys-429, Lys-416 or His-417 help to stabilize the one-chain form of tPA that is responsible for the higher activity of the tPA zymogen when compared to other members of the serine protease family, and indeed, the Lys-416, His-417 mutant shows lowest zymogen activity of all forms tested (figure 4, page 3454). Additionally, Peterson *et al.* teach that strong ligands such as fibrin and PAI-1 may stabilize the active conformational state more efficiently and thus compensate for the destabilization resulting from the disruption of the salt bridge formed with Asp-477 (page 3456, column 2, paragraph 3).

Lamba *et al.* teach that the salt bridge formed between Lys-429 and Asp-477 of tPA contributes to the unusually high catalytic activity of the one-chain form of tPA (see Abstract).

Bennett *et al.* teach a variant human tissue-type plasminogen activator wherein Arg-275 is substituted for the non-basic amino acid glutamate, which results in a tPA mutant of increased half-life (column 3, lines 38-50).

Anderson *et al.* teach a variant human tissue-type plasminogen activator wherein His-417 is substituted for the non-basic amino acid alanine (column 11, line 2). Anderson *et al.* also teach a variant human tissue-type plasminogen activator wherein Lys-429 is substituted for the non-basic amino acid alanine. Andersen *et al.* teach the use of variant tissue-type plasminogen

activator for use in the treatment of vascular disease (abstract), deep-vein thrombosis (column 2, line 38), or thromboembolic occlusion of blood vessels (column 4, line 10-25). Anderson *et al.* teach the pharmaceutical composition for the treatment of deep vein thrombosis or peripheral vascular disease, "bolus" doses, on the order of about 0.05 to about 0.2 mg/kg (column 18, lines 37-62).

Hassouna *et al.* teach a diagnostic kit containing tPA (column 2, line 16).

Together, the above references teach a variant human tissue-type plasminogen activator (tPA) wherein Arg-275 and at least one other basic amino acid residue in the serine protease region (defined as amino acids 264 to 527 on page 2 of the specification) is substituted with a non-basic amino acid, which results in the disruption of the salt bridge formed with Asp-477 (claim 1; see Strandberg *et al.*, Tate *et al.* and Peterson *et al.* above). These alterations in protein sequence of human tissue-type plasminogen activator result in variant with increase selectivity to fibrin, increased fibrin stimulation factor, increased zymogenicity and are less inhibited by PAI-1 (Strandberg *et al.* and Petersen *et al.*). The above references teach the substitutions as being made with the non-basic amino acids glutamate, glycine, alanine, serine and threonine. The above references teach pharmaceutical compositions of human tissue-type plasminogen activator for the treatment of thrombotic conditions (Anderson *et al.*; regarding claim 25) and for use in diagnostic kits (Hassouna; regarding claim 28). The above reference teach the dose of variant human tPA on the order of about 0.05 to about 0.2 mg/kg (Andersen *et al.*) The above references teach the method of making variant human tPA comprising the steps of tissue culture and purification (Strandberg *et al.* and Tate *et al.*, regarding claims 30-31).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make the above substitutions because the substitution of Arg-275 of tPA is well documented in the art as a means to prevent the proteotic conversion of one-chain tPA to the two chain form (Tate *et al.*). Additionally, it is well know that the formation of the salt bridge with Asp-477 contributes to the stabilization of the one-chain form and is responsible for the activity of the tPA one-chain zymogen (Peterson *et al.*). Additionally, each of the amino acids substitutions made in the prior art (acids glutamate, glycine, alanine, serine and threonine) represent all the categories of non-basic amino acids, and therefore all conservative substitutions would be obvious to one of ordinary skill in the art (claim 2). Such substitutions are known to increase the zymogenicity, fibrin stimulation factor, fibrin selectivity factor and effect inhibition of tPA by PAI-1 (Strandberg *et al.*). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make substitutions at positions Asp-477, Lys-277, Lys-429, Lys-416 or His-417 as these amino acids are considered important in the art for the formation of the salt bridge and disruption of the salt bridge will lead to increased zymogenicity, fibrin stimulation factor, fibrin selectivity factor and lessen inhibition of tPA by PAI-1 (Lamba *et al.*, Tate *et al.*, Petersen *et al.* and Strandberg *et al.*). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to optimize the substitutions that lead to the variants of Arg-275-Glu, His-417-Asp, Arg-275-Glu, His-417-Glu or Arg-275-Glu, Lys-429-Tyr (regarding claims 21 and 32), which possess the properties of zymogenicity of 75 or 100 regarding claims 3-4); fibrin stimulation factor of 10,000 or 20,000 (regarding claims 5-9); fibrin selectivity factor of 100 (regarding claims 15-17); and a PAI-1 inhibition reduced by a factor of 5, 9, or 200 (regarding claims 10-14).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to prepare a pharmaceutical composition containing the disclose varient tPA molecules in the composition and dose ranges taught by Andersen *et al.* (regarding claims 25-26) or in a diagnostic kit taught by Hassouna *et al.* (regarding claims 28). Additionally, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to make the above variants using the method taught by Strandberg *et al.* (regarding claims 30-31). The person of ordinary skill in the art would have been motivated to make the above substitutions because it would be desirable to provide a tPA molecule that will act only at the site of the clot and not systemically, such as, relative to wild type tPA, a tPA molecule that has a higher fibrin stimulated activity than fibrinogen stimulated activity. The person of ordinary skill in the art would have expected success because variants of tPA are made routinely in that art and the parameters to measure all will established (Stranberg *et al.*, Tate *et al.*, Petersen *et al.* and Lamba *et al.*). Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Advisory Information

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan K Snedden whose telephone number is (703) 305-4843. The examiner can normally be reached on Monday - Friday, 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 746-3975 for regular communications and (703) 746-3975 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SKS
September 9, 2002

SKS

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600